JOURNAL OF MODERN NEUROLOGY
http://www.physi-med.com

ORIGINAL RESEARCH ARTICLE

High-Sensitivity C-reactive Protein on Severity And Prognosis of Symptomic Middle Cerebral Artery Atherosclerotic Stenosis

Cao JX[1], Jiang JD[1], Liu L[1], Liu H[1], Zhuang AX[1], Geng DQ[2]

[1]*Department of Neurology,Lianyungang City Second People's Hospital Sinpo District*
[2]*Department of Neurology, affiliated Hospital of Xuzhou Medical University*

ARTICLE INFO

Article history:
Received: 21 Sep, 2015
Revised: 5 Feb, 2016
Accepted: 14 Feb, 2016
Published online: 16 June, 2016

Keywords:
C-reactive protein; symptomic middle cerebral artery atherosclerotic stenosis; MR angiography; Prognosis

ABSTRACT

Objective: To investigate the relationship between high-sensitivity CRP(hs-CRP) and poor outcome (modified Rankin Scale score>2) or end point events at 3 months in the patients with symptomic middle cerebral artery atherosclerotic stenosis (SMCAAS). Methods: One hundurd and twenty-three consecutive patients with SMCAAS were admitted within 72 hours of symptom onset. hsCRP and NIH stroke scale (NIHSS) were measured at the time of admission. Patients were followed for up to 3 months for Short-term functional outcome measured by mRS and end point events. Logistic regression model was applied to adjust for confounding variables. Results: patients with hs-CRP levels >3 mg/L had high NIHSS (P< 0.001)and poor short-term functional outcomes or end point events (p=0.01; p=0.03). After adjusting for confounding variables, high hs-CRP remained to be associated with high end point events (p =0.033)at 3 months only.Conclusion: admission hs-CRP concentration is an independent predictor of end point events at 3 months when measured within 72 hours after onset of SMCAAS.

Atherosclerotic intracranial artery stenosis is Chinese main cause of ischemic cerebral apoplexy, mainly happened in the middle cerebral artery (MCA), which have high rate of relapse [1-2].There are also did not reach satisfactory curative effect even with regular cure in the treatment of atherosclerosis intracranial artery lesions [1-2]. Discuss the disease severity and prognosis related serological indicator has important practical significance. C-reactive protein (C - reaction protein, CRP) is an indicator which has a lot of research in atherosclerosis and cardiovascular disease risk factors in recent years, and it is one of the mark of vascular disease prognosis and future vascular

First Author: Cao JX, Department of Neurology,Lianyungang City Second People´s Hospital Sinpo District, Hai Lian Road 41,Lianyungang 222006, Jiangsu Province, China.
Corresponding Author: Deqin Geng, Department of Neurology,affiliated Hospital of Xuzhou Medical University.
E-mail:gengdeqin@hotmail.com

events [3]. Intracranial atherosclerotic stenosis also exist inflammation process [4]. But less study on the relationship of disease severity and prognosis of CRP and symptomatic intracranial artery stenosis that due to the recurrence of symptomatic intracranial artery stenosis is high in the early phase[5-7]. this study aims to investigate allergic C - reactive protein (High sensitivity C - reaetive protein, hsCRP) for symptomatic middle cerebral artery artery stenosis condition judgement and predictive value of short-term prognosis. This study aims to investigate the predictive value of condition judgement and short-term prognosis of high sensitivity C - reaetive protein (hsCRP) for the artery and main artery stenosis in symptomatic middle cerebral.

1. Materials and Methods

1.1 General Information

One hundurd and twenty-three cases of symptomic middle cerebral artery atherosclerotic stenosis which had been confirmed by TCD and MRA and clinical diagnosis were seclected from September 2008 to March 2011.All patients were attacked within 72 hours. There were 76 cases of male and 47 cases of female, 40 to 87 years old, the average was (69.3 ± 11.2) years old. At the same time, DWI examination confirmed that new infarcts in narrow MCA blood supply area, of 40 or higher. The clinical data of patients and main risk factors of stroke were record, including hypertension, diabetes mellitus (DM), coronary heart disease, high cholesterol, smoking, drinking, family history of stroke and carotid plaques. All of the patients into the team had been complete the plasma hs - CRP examination and the national institutes of health stroke Scale score (NIHSS), Follow-up and modified Rankin Scale score 3 months after treatment (modified Rankin Scale, mRS > 2 is divided into poor prognosis index) and end events incidence. End point events including the primary end point (TIA) and cerebral infarction, secondary end points (acute angina and myocardial infarction) and all-cause death.

1.2 Methods

1.2.1 The Determination of Serum hs-CRP

Patients on an empty stomach were taken 3 mL venous blood serum into the group the next morning in the hospital. Sucked out serum after centrifugal and then application of automatic special protein analyzer which came from Beckman companies in the United States. hsCRP kit purchased from the company, using immune scattering turbidimetric method for the quantitative determination. All the test was inspection independently by one not familiar with the clinical data of patients, and in strict accordance with the kit instructions and equipment operation procedures, normal for (0-3) mg/L, greater than 3 mg/L is above the average, hsCRP acuity 9.5 mg/L may consider merging potential infection on admission, not included in the analysis.

1.2.2 Head MRI

Using Siemens l. 5 t superconducting magnetic resonance system, all patients had been accepted to checked by MRI (conventional MRI DWI) and three-dimensional time leap method of magnetic resonance angiography (3 d TOF MRA) MRA examination within 5 d after attack, and routine MRI including T1 weighted and T2 weighted and FLAIR sequence line transverse, sagittal scans, and MRA examination including intracranial vascular. A vice director of radiology and two high qualification neurologist read MRI film together, and two consecutive DWI in high intensity signal at least can be regarded as acute cerebral infarction.

1.2.3 MCA Stenosis Criterion

Standard of MRA in the diagnosis of MCA stenosis:The degree of tube cavity stenosis and signal loss were based upon MRA display, according to the standard of Gao etal [8]to evaluate the degree of vascular stenosis [8]. More than 50% of cerebral artery stenosis was defined as a meaningful narrow lesions in this study and excluded patients with extracranial stenosis of 50% or higher. The blood flow velocity of MCA stenosis was diagnosed by TCD have some condition as follows. All patients had been accepted to checked by TCD examination within 5 d after attack. The peak systolic blood flow velocity ≥ 140 cm/s and the mean flow velocity (MFV) ≥ l00 cm/s with spectrum disorders and/or vortex noise suggest there may be a MCA stenosis. The existence of the MCA stenosis must be confirmed with TCD and MRA examination for all patients, and recorded other intracranial artery stenosis whether there have at the same time.

1.2.4 Statistical Treatment

The data entry and statistics analysis were been used SPSS 13.0 statistical software. Normal distribution variables adopt mean description, t test. Non-normal distribution variables adopt the median and interquartile range description, non-parametric test. Count data using x2 test, small sample using the Fisher 's inspection, correlation analysis using spearman correlation analysis method, multiple factors analysis using Ligistic regression analysis, P values < 0.05 were all statistically significant.

2. RESULTS

2.1 General Information

Five hundred and eighty-nine cases of hospitalized patients which were clearly diagnosed as cerebral infarction were selected. The eligible patients with symptomatic MCA stenosis were 123 cases, with 108 cases in the form

of cerebral infarction(87.8%), 15 cases in the form of TIA (12.2%). The risk factors of symptomatic MCA stenosis apoplexy were 87 cases of hypertension (70.7%), 41 cases of diabetes(33.3%), 68 cases of hyperlipidemia(55.3%), 25 cases of coronary heart disease(20.3%), 58 cases of smoking(47.2%), 32 cases of alcoholism (26.0%), 31 cases of family history of stroke (25.2%). The values of hs-CRP were abnormal distribution, the range of 0.14-8.84 mg/L, the median of 2.17 mg/L, and the interquartile range of 1.06-4.54 mg/L. The patients were divided into the normal hs-CRP group (hs-CRP≤ 3 mg/L) and (hs-CRP > 3 mg/L) compares two groups of patients, respectively. There were 44 cases in the hs-CRP increased group (35.8%), and their stroke risk factors such as diabetes mellitus and smoking ratio is higher than the normal hs-CRP group (Table 1).

Table 1 The basic information of symptomatic MCA stenosis patients

	The normal hs –CRP group (79 cases)	The hs –CRP increased group (44 cases)	P 值
Age mean (SD)	65.39(9.83)	66.77(9.69)	0.45
gender(male)	47/32	29/15	0.48
Diabetes n (%)	20(25.3%)	21(47.7%)	0.01
Blood pressuren (%)	54(68.4%)	33(75.0%)	0.44
Hyperlipidemian (%)	41(51.9%)	27(61.4%)	0.31
Smoking n (%)	31(39.2%)	27(61.4%)	0.02
Drinking n (%)	19(24.1%)	13(29.5%)	0.51
Coronary heartdi –sease (CHD)n (%)	12(15.2%)	13(29.5%)	0.06
Family history of stroke n (%)	19(24.1%)	12(27.3%)	0.69
NIHSS, mean (SD)	2.33(1.56)	3.46(1.19)	0.001
MRS > 2, n (%)	24(30.4%)	28(63.6%)	0.001
Recurrent stroke n (%)	4(5.1%)	8(18.2%)	0.027
All –cause mortality n (%)	2(2.5%)	3(6.8%)	0.348
Endpoint events	6(7.6%)	11(25.0%)	0.007

2.2 The relationship between hs-CRP and illness severity of SMCAAS

The SMCAAS illness severity through expression NIHSS score when patients entering the group, NIHSS score were abnormal distribution, range of 0 to 6, the median of 3, the interquartile range of 2-4. NIHSS score of the hs-CRP increased group was obviously higher than that of normal hs-CRP group ($P < 0.001$; rank-sum test, see table 1). Correlation analysis results showed that the hs-CRP levels and NIHSS scores were positively correlated ($r = 0.454$, $P < 0.001$; Spearman 's related).

2.3 The relationship between hs-CRP and short-term prognosis of SMCAAS

Three months follow-up after treatment. Degree of functional recovery in patients were mRS score, and mRS score of abnormal distribution, range of 0 to 5, the median of 2, the interquartile range of 1-3. NIHSS score of the hs-CRP increased group was obviously higher than that of normal hs-CRP group ($P = 0.001$; rank-sum test), and the incidence of poor prognosis was significantly higher than normal hs-CRP group (63.6% ,30.4% ;$P = 0.001$; OR4. 01,95% CI1.84~8.74). Logistic regression analysis, the hs-CRP > 3 mg/L was not independent risk factor for poor prognosis ($P = 0.69$). There were 17 cases of outcome event (13.8%), 12 cases recurrent stroke (9.8%), 5 cases died (4.1%) follow-up of 3 months including 4 cases of vascular factors, 2 cases of cerebral infarction recurrence, 1 case of myocardial infarction, 1 case of lower limb arterial thrombosis, 1 case of vascular factors and 3 cases pulmonary infection. The endpoint events of the hs-CRP increased group was significantly higher than that of normal hs-CRP group (25.0% ,7.6% ;P=0.007，0R4.06,95% CI1. 38~11.89). Control other confounding factors such as gender, age, hypertension, diabetes, hyperlipidemia, coronary heart disease, smoking, drinking, family history of stroke, NIHSS score, etc. Logistic regression analysis, the hs-CRP > 3 mg/L (OR3.98;95% CI1.12-14.23;P=0.033) was independent risk factor for SMCAAS endpoint events.

3. DISCUSSION

The NIHSS score of the hs-CRP increased group is sig nificantly higher than that of normal hs-CRP group in pa tients with symptomic middle cerebral artery atherosclerotic stenosis（SMCAAS）at admission according to the results of this study, and the mRS score, poor prognosis, recurrence of ischemic vascular lesions and the risk of death are significantly higher than the normal group follow-up of 3 months. This result corrected other cerebrovascular disease risk factors after the acute phase of the hs-CRP increased is still closely related to the endpoint event for the independent risk factors, and the hs-CRP increased have 3.98 times risk of occurring endpoint events than not increased (P=0.033). These results suggest acute hs-CRP levels are closely related to SMCAAS condition and short-term prognosis risk predictors.

As acute inflammatory reaction protein, CRP is minimal content in the serum or plasma under normal circum-

stances. There is acute inflammation in the body with elevated serum CRP concentration can be quickly into one hundred times. Numerous studies have found that atherosclerosis is a chronic inflammation, it would make the serum CRP level slightly increased continuously, 3 to 10 mg/L, more conventional CRP detection (detection lower limit of 8-10 mg/L) cannot complete, and the hs-CRP detection (detection range 0.01 10.00 mg/L) can improve the sensitivity of determination of CRP. Past studies have shown that the increase of serum CRP concentration is one of the independent risk factors for cardiovascular disease [3-9]. The reason is the hardening of the arteries in intracranial and extracranial or coronary atherosclerosis have certain difference[10]. The study of relationship between hs-CRP and intracranial atherosclerosis especially with SMCAAS is less, and the detection time and follow-up time are also not consistent[4-6]. Arenillas et al[6] in Europe people study found CRP level after 3 months was related to prognosis risk of followed up for 1 year symptomatic intracranial artery stenosis, and found that elevated levels of CRP was associated with intracranial atherosclerosis progression independent [4]. Intracranial atherosclerosis dynamic had evolution process, intracranial atherosclerosis progression was closely related with recurrence of ischemic vascular lesions and to the risk of death, support the results[4-11].

The hs-CRP levels of SMCAAS acute SMCAAS illness severity of short-term prognosis related mechanism is not clear, may be that SMCAAS in the acute phase serum hs-CRP reflects the degree of brain tissue damage and individual levels of inflammation, hs-CRP increased in acute phase on behalf of the brain tissue damage which has strong inflammatory reaction so that the illness is heavier, and the risk of cardiovascular disease the future recurrence would be also increased [3-6, 9]. The hs-CRP increased by inflammatory mechanisms to promote vascular endothelial injury and intracranial atherosclerosis progress, and is closely related to the recurrence of ischemic vascular disease and mortality risk [9-14]. The hs-CRP increased are also directly damage the blood-brain barrier, promote the brain tissue damage [15].

Intracranial atherosclerosis is the major cause of stroke in Asian populations, especially in the brain artery stenosis or occlusion, and there is still lack of ideal treatment. The effective evaluation and screening high-risk patients with SMCAAS and predict its prognosis have important theory value and practical significance. The results show the risk of again hair ischemic vascular lesions and death for the SMCAAS patients who hs-CRP levels increased was significantly higher than that of normal hs-CRP within 3 months. These results suggest acute hs-CRP levels are closely related to SMCAAS condition and short-term prognosis risk predictors.These results have important significance in the treatment and secondary prevention of SMCAAS in the future. More attention should pay to detection the level of hs-CRP and intervention hs-CRP levels in early phase for SMCAAS treatment process. The instability of intracranial atherosclerosis plaque should be using anti-inflammatory intervention therapy according to the hs-CRP level might improved the prognosis of SMCAAS, and more research need to be given in the further[16].

REFERENCES

1. Komotar RJ, Kellner CP, Raper DM, et al. PM.Update on the natural history of intracranial atherosclerotic disease: A critical review.World J Radiol. 2010 ;2(5): 166–171.

2. Samaniego EA, Hetzel S, Thirunarayanan S, et al. Outcome of symptomatic intracranial atherosclerotic disease.Stroke. 2009;40(9):2983–2987.

3. Schlager O, Exner M, Mlekusch W, et al.C–reactive protein predicts future cardiovascular events in patients with carotid stenosis.Stroke. 2007;38(4):1263–1268.

4. Arenillas JF, Alvarez–Sabín J, Molina CA, et al. Progression of symptomatic intracranial large artery atherosclerosis is associated with a proinflammatory state and impaired fibrinolysis.Stroke. 2008 ;39 (5): 1456–1463.

5. Arenillas JF, Massot A, Alvarez–Sabín J, et al. C–reactive protein gene C1444T polymorphism and risk of recurrent ischemic events in patients with symptomatic intracranial atherostenoses. Cerebrovasc Dis. 2009;28 (1):95–102.

6. Arenillas JF, Alvarez–Sabín J, Molina CA, et al. C–reactive protein predicts further ischemic events in first–ever transient ischemic attack or stroke patients with intracranial large–artery occlusive disease.Stroke. 2003 ;34(10):2463–2468.

7. Ovbiagele B, Cruz–Flores S, Lynn MJ, et al. Early stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis. Arch Neurol. 2008 ;65(6):733–7.

8. Shan G, Huang JX, Huang YN et al. Epidemiological investigation and check method of intracranial artery stenosis.zhongguo yixue kexueyuan xuebao,2003,25 (1): 96–100.

9. Elkind MS, Luna JM, Moon YP, et al.High–sensitivity C–reactive protein predicts mortality but not stroke: the Northern Manhattan Study. Neurology. 2009;73(16): 1300–1307.

10. Man BL, Fu YP, Chan YY, et al. Lesion patterns and stroke mechanisms in concurrent atherosclerosis of

intracranial and extracranial vessels.Stroke. 2009 ;40 (10):3211–3215.

11. Arenillas JF, Molina CA, Montaner J, et al. Progression and clinical recurrence of symptomatic middle cerebral artery stenosis: a long–term follow–up transcranial Doppler ultrasound study.Stroke. 2001;32 (12):2898–2904.

12. Youn CS, Choi SP, Kim SH, et al. Serum highly selective C–reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. Am J Emerg Med. 2010 Dec 13.

13. Purroy F, Montaner J, Molina CA, et al. C–reactive protein predicts further ischemic events in transient ischemic attack patients.Acta Neurol Scand. 2007 ;115 (1):60–66.

14. Kuhlmann CR, Librizzi L, Closhen D, et al. Mechanisms of C–reactive protein–induced blood–brain barrier disruption. Stroke. 2009;40(4):1458–1466.

16. Chan YH, Lau KK, Yiu KH, et al..Reduction of C–reactive protein with isoflavone supplement reverses endothelial dysfunction in patients with ischaemic stroke. Eur Heart J. 2008 ;29(22):2800–2807.